REMARKS

The pending claims (claims 13, 15-17, 19-24, 26-32, 34-43, 45-52, 54-62 and 64-68) remain directed to a combination therapy invention (method and related pharmaceutical composition) described by the pending application. The claims are directed specifically to methods and compositions wherein the COX-2 inhibitor, or its pharmaceutically acceptable salt, is used in combination with a lipid lowering drug.

Pursuant to the recent interview, claims 13, 40, 49 and 59 have been amended to clarify that the following conditions: coronary artery disease, arteriosclerosis, atherosclerosis, myocardial infarction, stroke, thrombosis, angina, coronary plaque inflammation, bacterial induced inflammation, viral induced inflammation and inflammation associated with surgical procedures are included in the cardiovascular disorders against which the preventative method of the present invention is directed. As a consequent of these amendments, claims 18, 44, 53 and 63 have been cancelled and claims 19, 45, 54 and 64 have been amended to correct their dependency. No new matter is added.

As discussed at the interview, Claims 24, 40 and 49 also have been amended to clarify that applicants are claiming the prophylactic use of their combination therapy invention, *i.e.*, the combined use of a COX-2 inhibitor and a lipid lowering drug as a therapy for those at risk of developing a cardiovascular disorder, in order to reduce or minimize a subject's risk of developing a cardiovascular disorder. As described in the application, the word "prevention" embraces the "prophylactic treatment of those at risk of developing a cardiovascular disorder," see page 3 of the application. One of the definitions of prophylactic is "tending to prevent or ward off disease." It is this aspect of the disclosed invention that applicants intend to embrace with the pending claims and thus this minor amendment is supported by the application.

Entry of these amendments under Rule 116 is respectfully requested. These amendments could not have been presented earlier, since they are made in response to a rejection challenging the enablement of the claims, a rejection that was FIRST made in the final office Action.

The Office Action has examined claims directed to a combination therapy of a lipd

lowering drug (specifically (1) an IBAT inhibitor, (2) a fibrate, (3) niacin, (4) a statin, (5) a CETP inhibitor or (6) a bile acid sequestrant) and a COX-2 inhibitor, including independent claims 13, 24, 40, 49 and 59. Composition claims 32 and 34-39 have been withdrawn from further consideration.

As a preliminary matter, applicants would again like to alert the Examiner to Dellaria et al., U.S. Patent 5,776,984, as was done at the recent interview. This document is listed on an attached form PTO-1449 and a copy is provided with this amendment. In view of the circumstances outlined below, applicants request that this document be considered and entered into the record of this examination/prosecution. Applicants became aware of this document when this document was cited in an Office Action (dated April 9, 2003) issued by Examiner Jagoe (the same Examiner who examined the subject application) in the related continuation application (S.N. 09/946,623) of the subject application. The Office Action in the continuation application was issued (April 9, 2003) a day after the Office Action was issued in this application (April 8, 2003). Examiner Jagoe is examining both applications (the subject application and the related continuation) and as noted cited the Dellaria '984 patent in the continuation application a day after issuing the present Office Action. Accordingly, Examiner Jagoe is aquanted with the '984 patent and its potential applicability to the pending application and claims. Nonetheless, applicants refer it to the examiner's attention out of an abundance of caution and in the hope of correcting Examiner Jagoe's apparent inadvertence in not making it of record in both applications. If any fee needs to be paid in order to cite this patent as part of the present record, applicants' undersigned representative asks that Deposit Account No. 19-0733 be charged for any required fee.

According to the Office Action, "[t]he rejections in paper numbers 13 and 19 are maintained and are hereby repeated." As discussed at the interview, it is the undersigned's belief that the only rejection that is currently in the case stemming from rejections made in the earlier-cited papers is the 35 U.S.C. 103(a) rejection of the claims. This rejection will be dealt with later in this amendment. The earlier (1) 35 U.S.C. 102 anticipation rejection of now-cancelled claims 1-12; (2) the 35 U.S.C 112, para 2 rejection of claims 17-23, 28-31 and 36-39 and (3) the 35

U.S.C. 112, para. 1 written description rejection of claims 40-58 made earlier have all be implicitly withdrawn.

Claims 40 (and presumably its dependent claims), 49 (and presumably its dependent claims) and 59 (and presumably its dependent claims) stand rejected under 35 U.S.C. 112, first paragraph.

Each of these rejections is respectfully traversed.

While the Office Action separates these rejections along the line of the three separate independent method claims, even the most cursory reading of the support provided in the Office Action for each rejection makes it apparent that each rejection is premised on the same purported facts and argument. For that reason, and in the hope of reducing redundancy, we will generally treat the rejections together.

The Office Action contends that the claimed invention is "extremely complex" because it "encompasses the actual prevention of a cardiovascular disorder." This contention does not have any factual support in the Office Action. Actually, the invention is relatively simple and straigtforward. Two of its main components, the COX-2 inhibitor and the various lipid-lowering co-therapeutic agents are known materials and are known to have therapeutic utilities on their own merit (indeed this appears to be the basis for the obviousness rejection addressed later in this response). As described in the application, see pages 28-32 in particular, there are taught a wide range of treatment modalities and available formulations for practicing the invention. Those skilled in the art will have no difficulty designing myriad treatment scenarios, particularly given the information that was readily available to those skilled in the art for use of the individual agents at the time the application was filed.

The Office Action also contends that the claim is very broad. Again, factual support for this contention is lacking. The operative step of the claimed invention is "treating" a subject with a therapeutically effective amount of a COX-2 inhibitior and one of the recited co-therapeutic lipid-lowering agents, a process which is focused and defined. Apparently, the contention of breadth is linked to the fact that any particular cardiovascular disease itself may have many different causes and not all of these causes are necessarily "addressed by

administration of the claimed compounds." The fact that cardiovascular disease may have many different causes is unrelated to claim scope. Similarly, the fact that the claimed therapeutic agents may not act as an intervention for these many different causes also is unrelated to claim scope. Indeed, how the invention works to reduce a subject's risk of developing a cardiovascular disorder is not a question of claim breadth; indeed it is not even something that must be described in a patent application.

The Office Action contends that the specification provides only minimal guidance on how to administer the therapeutic agents and is lacking in working examples. Working examples are not required (See *In re Borkowski,* 164 USPQ 642 (CCPA 1970)) and the description provided by pages 28-32 of the application provides ample guidance on how to administer the recited therapeutic agents to a patient. As the Office Action acknowledges, the state of the art is "relatively high" with regard to the treatment of the conditions embraced by the term cardiovascular disorders. Such highly skilled workers can adequately administer the co-therapeutic agents to acheive the objectives of the invention. In this regard, it appears that the Office Action is trying to draw some distinction between "treatment" and the prophylactic objectives of the present invention, and that the application's focus on prophylaxis subjects the claimed invention to a higher standard than treatment claims would be. That is unwarranted, particular as it pertains to the pending claims

The Office Action appears to acknowledge that the application enables the prophylactic treatment of atheroscelerosis. The Office Action contends that the application does not enable the prophylactic treatment of a cardiovascular disorder (generic scope).

It appears that the Office Action is seeking proof that the claimed method completely prevents the onset of any and all cardiovascular diseases. If true, this is not only an unfair requirement, but exceeds the bounds of what an examiner can reasonable request in view of the scope and content of the pending claims. In the first place, claim 59 does not even use the word "preventing" or any modified version of that word. In the second place, in those claims in which the word "preventing" previously appeared, *i.e.,* claims 24, 40 and 49, it is clear from the context of the claim that the word is used in connection with the concept of prophylaxis, *i.e.*, "tending to

prevent or ward off disease" and the claims now have been amended consistent with that intent. In such context, requiring proof of the absolute is simply not appropriate.

Thus, while couched in terms of enablement, the rejection actually appears to be a masked utility rejection, *i.e.*, a disbelief that the claimed combination therapy will successfully ameliorate the risk of the development, or further progression, of a cardiovascular disease effectively.

The application clearly discloses the compounds that are to be used in the combination therapy. The application also provides specific description of doses of the COX-2 inhibitors to employ. The related doses of the lipid-lowering drugs are simply those doses used for these well-known materials in the prior art. These teachings, considered within the context of the skilled worker, adequately enable those one skilled in the art to practice the claimed therapy.

Whether the therapy will successfully result in a lowered incidence of cardiovascular disease is a separate issue, and on this point the evidence in the specification, and the supporting evidence submitted with this response, is sufficient to satisfy the statutory requirements. *In re Brana*, 34 USPQ2d 1436 (Fed. Cir. 1995). In *Brana*, a §112 ¶1 rejection was reversed in circumstances akin to those present here.

Under these circumstances, the Patent Office's doubts regarding the success of the claimed prophylactic co-therapy would be unreasonable.

While there is no requirement that an applicant provide data from human clinical trials to establish utility for an invention related to the treatment of human disorders, even with respect to situations where no art-recognized animal model exists for the human disease encompassed by the claims, applicants now provide some evidence for the Examiner's consideration.

Enclosed with this response are (1) D. Dudek et al., "More pronounced decrease of inflammatory markers with combination of statins and COX-2 inhibitors following acute coronary syndromes," *European Heart Journal*, Vol. **22**, Abstr. Suppl. September 2001, p. 240 – 60 and (2) Chenvard et al., *Circulation*, **107**:405-409 (2003). As discussed at the recent interview, the articles (1) and (2) describe human clinical trials that evaluated the effect of selective COX-2 inhibitors (in both cases in combination with a statin) for treating a

cardiovascular disorder. For the examiner's convenience, these documents are listed on the attached form PTO-1449 even though they relate to post-priority filing activity.

In the 2001 summary report, patients with unstable angina after successful percutaneous coronary intervention treatment were divided into three groups (1) atorvaststin 10mg/day for six months (2) atorvastatin 40mg/day for six months, and (3) atorvastatin 40mg/day for six months PLUS rofecoxib (a COX-2 inhibitor) 12.5mg/day for first three months. Patients also received aspirin and ADP receptor blocker. As reported, the invenstigators observed a more pronounced decrease of inflammatory markers in patients treated with combination of statin and COX-2 inhibitor. The summary reports that the addition of COX-2 inhibitor to standard statin therapy seems to be safe and effective in reduction of inflammatory markers concentration in patients following percutaneous coronary intervention treatment due to acute coronary syndromes.

In the study reported in the 2003 article, 14 patients (13 completed the study) were given either (a) a combination of aspirin and a statin, or (b) a combination of aspirin, a statin and celecoxib (a COX-2 inhibitor) for a period of two weeks. The investigators concluded that the study demonstrated that a selective COX-2 inhibitor coupled with the standard therapy (included a statin) improves endothelial function and reduces markers of inflammation and oxidative stress in patients with coronary artery disease. "[T]he improvement of endothelial function and the reduction of hs-CRP and ox-LDL in the present study were observed on top of background therapy with aspirin and **statins** in **all** patients..." (emphasis added).

In addition, U.S. 6,245,797 (previously cited in the prosecution of this application), which issued on June 12, 2001 (Primary Examiner Dwayne C. Jones), claims *inter alia,* a method for reducing the risk of developing atherosclerotic disease by using a combination of an HMG-CoA reductase inhibitor (a statin) and a COX-2 inhibitor. Applicants maintain that the prior issuance of this patent is additonal evidence of the utility/enablement of the subject matter embraced by the pending claims. By virtue of the April 18, 1997 filing date of the provisional application on which the subject application claims benefit, however, the '797 patent is not citable against the subject application as prior art under §§102 and 103 of the Patent Statute.

Moreover, under the Utility Examination Guidelines, 60 FR 36263 (7/14/95), "a previous lack of success in treating a disease or condition . . . should not standing alone, serve as the basis for challenging the asserted utility . . . "

In light of the proffered results, one skilled in the art would understand that the claimed therapeutic methods would be useful in the prophylatic treatment of individuals at risk of cardiovascular diseases.

Therefore, Applicants respectfully submit that the rejected claims are enabled, and request that the rejection of these claims under 35 U.S.C. §112, first paragraph be withdrawn.

All pending claims are believed to stand rejected under 35 U.S.C. 103 as being unpatentable over a combination of WO 95/15316 (Searle) taken in combination with the Merck Manual, Section 2, Chapter 15, Hyperlipidemia (http://www.merck.com/pubs/mmanual/section2/chapter15/15c.htm). This rejection is respectfully traversed.

WO 95/15316 directed to substituted pryrazolyl benzesulfonamides for the treatment of inflammation. This WO publication teaches that the recited compounds, a particular class of selective COX-2 inhibitors, are useful for the treatment of inflammation (page 7, lines 8-10). This WO publication specifically teaches that "[c]ompounds of Formula I would be useful in treating inflammation in such diseases as vascular diseases ... myocardial ischemia and the like" (page 7, lines 27-36).

The Merck Manual reports that aggressive cholesterol lowering with statins has been shown to prevent unstable angina and MI and decrease the need for surgical coronary revascularization. Pointedly, the Merck manual specifically cautions about risk of combo therapy, and is noteably silent about con-joint use with anti-inflammatory drugs, let alone the COX-2 inhibitors required by the pending claims.

The combination rejection posed by the Office Action is based on an improper hindsight evaluation of the invention defined by the pending claims. The Office Action completely ignores issues of adverse interaction that potentially precludes combination therapies, a warning expressly recited in the cited Merck Manual with respect to certain co-therapies. Instead, the Office Action has selected the cited references purely from a hindsight consideration of

applicants' pending claims. This is improper. It is black letter law that a combination constructed from hindsight does not present a prima facie case of obviousness. The Office Action's sole justification for selecting these disparate disclosures for consideration in combination was that they each teach compositions to be useful for the same purpose. However, those skilled in the pharmaceutical arts recognize that adverse drug interactions is always a possibility and broad teachings to use one drug for a specific indication does not make it obvious to use it in combination with any and all other drugs potentially suitable for the same or a similar indication.

Furthermore, there is additonal evidence that must be considered that supports the patentability of the pending claims.

First of all, the prior issuance of the '797 patent underscores the patentability of the subject matter embraced by applicants' pending claims, since substantially that same subject matter had already been considered to be patentable by the USPTO (in the issued '797 patent) and thus must be patentable over the cited combination of documents. The same combination of documents cited in the present Office Action would be prior art to the '797 patent. Indeed, the possible need for instituting an interference between the '797 patent and the pending application was specifically discussed in previous correspondence and a previous interview.

Additonal evidence of patentability is found in D. Dudek et al., *European Heart Journal*, Vol. **22**, Abstr. Suppl. September 2001, p. 240 – 60 and and Chenvard et al., *Circulation*, **107**:405-409 (2003). As noted above, these articles describe human clinical trials that evaluated the effect of selective COX-2 inhibitors (in both cases in combination with a statin) for treating a cardiovascular disorder, see the enclosed form PTO-1449.

The 2001 article provides a summary report that the addition of COX-2 inhibitor to standard statin therapy seems to be safe and effective in reduction of inflammatory markers concentration in patients following percutaneous coronary intervention treatment due to acute coronary syndromes.

The investigators report in the 2003 article that the study demonstrated that a selective COX-2 inhibitor coupled with the standard therapy (included a statin) improves endothelial

function and reduces markers of inflammation and oxidative stress in patients with coronary artery disease. "[T]he improvement of endothelial function and the reduction of hs-CRP and ox-LDL in the present study were observed on top of background therapy with aspirin and **statins** in **all** patients..." (emphasis added).

In light of the hindsight nature of the rejection, this information demonstrates the patentability of the subject matter defined by the pending claims.

On the basis of the foregoing, prompt consideration of all claims in the subject application is respectfully requested.

Respectfully submitted,

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